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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/581,044	06/08/00	LEE	T TSRI609.1

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EXAMINER	
RUSSEL, J	
ART UNIT	PAPER NUMBER
1653	12

DATE MAILED: 10/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/581,044	T. Lee et al
Examiner	**Group Art Unit**
J. Russel	1653

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 6-28-2001 and 7-17-2001.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1, 3, and 6-23 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) 6-9 and 19-22 is/are allowed.

☒ Claim(s) 1, 3, 10, 12-15, and 23 is/are rejected.

☒ Claim(s) 11 and 16-18 is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

1. The sequence listing filed June 28, 2001 has been approved.

2. The clean copy and the marked-up copy of the amended claims filed June 28, 2001 are not identical. In particular, the proviso inserted at the end of claim 1 is not the same in each copy. Any future amendments should be carefully reviewed in order to ensure compliance with the amendment rule

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: The claim for priority is not the first sentence of the specification. The first sentence inserted into the specification by the amendment filed June 28, 2001, referring to the language of the parent PCT application, should be deleted and its substance incorporated into the actual claim for priority.

3. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite because the proviso addresses a situation in which R_2 is hydroxyl, but there is no indication in the definition of R_2 in the main body of the claim that R_2 can ever be hydroxyl.

4. Claim 1 is objected to because of the following informalities: At claim 1, second-to-last line, "or" should be inserted between "R_2" and R_3", "the" should be changed to "then", and "nor" is misspelled. Appropriate correction is required.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claim 1 is rejected under 35 U.S.C. 103(a) as being obvious over the European Patent Application '145. The European Patent Application '145 teaches an HIV-protease inhibitor at page 3, lines 25-32, and page 10, lines 1-19, which differs from Applicant's claimed protease inhibitors in that the European Patent Application '145, for the compound of page 10, does not specifically teach X being methylene, R_{21} and R_{22} being H, and R_3 being t-butyl, although these possibilities are embraced by the generic formula at page 3. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form a compound according to the European Patent Application '145 in which X is methylene, R_{21} and R_{22} are H, and R_3 is t-butyl, because these possibilities are embraced by the generic formula, because the choice of X being methylene and R_{21} and R_{22} being H results in the presence of a conventional proline residue, because the choice of R_3 being t-butyl is the choice of homologous small alkyl groups, and because the resulting compound has only the expected protease inhibitory activity.

7. Claim 23 is rejected under 35 U.S.C. 102(b) as being anticipated by the Dreyer et al article. The Dreyer et al article at page 941, Table II, compound XI, teaches a protease inhibitor which has the same structure as the compound recited in Applicant's claim 23.

8. Claim 3 is rejected under 35 U.S.C. 103(a) as being obvious over Handa et al. Handa et al at Example 85 teach a compound which has the same structure as the compound recited in Applicant's claim 3, except that Handa et al's compound comprises a cysteine residue rather than a valine residue. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the compound of Handa et al with a valine residue rather

than a cysteine residue, because Handa et al disclose an alkyl sidechain to also be a preferred substituent at the same position as the asparagine sidechain (see column 5, lines 14-16), because valine is also a commonly available and well-known amino acid, and because the resulting compound has only the expected protease inhibitory activity. Handa et al's compound of Example 85 with its 3(S)-2(R) configuration has the same stereochemistry required by Applicants' claim 3. Handa et al do not teach the compound of Example 85 in stereochemically pure form, but in general disclose producing optically pure forms (see, e.g., column 4, lines 60-65, and column 8, lines 49-53). It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the stereochemically pure compound of Handa et al as discussed above because Handa et al disclose the formation of optically pure forms, because it is desirable in the pharmaceutical arts to produce optically pure forms in order to avoid unwanted side effects from the other stereochemical forms and in order to increase the specific activity of the desired stereochemical forms, and because it is prima facie obvious to purify a known product. See MPEP 2144.04(VII).

9. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by the Tam et al article. The Tam et al article teaches compound 3 (see Table I) which corresponds to Applicants' compounds of claim 1 in which R_1 is carbobenzoxy, R_2 is CH_2-Phenyl, and R_4 is -H(t-Butyl).

10. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application '100. The WO Patent Application '100 teaches compound 17-R (see page 49) which corresponds to Applicants' compounds of claim 1 in which R_1 is carbobenzoxy, R_2 is CH_2-Phenyl,

R_3 is hydrogen, R_4 is hydroxyl, R_5 and R_6 are a single combined oxygen forming a carbonyl group, and R_8 is -H(t-Butyl).

11. Claims 10, 12-15 and 23 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application '948. The WO Patent Application '948 teaches compounds 9, 108, and 125 (see pages 32 and 33) which differ from Applicants' claimed compounds of claims 10, 12-15, and 23 in the substitution of valine or leucine residues for the alanine residues. The WO Patent Application '948 teaches in general that Ala, Leu, and Val can be used in these sections of the compounds, designated by the reference as $(B)_n$ (see page 3, lines 1-8). It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form compounds according to the WO Patent Application '948 which have the structure of compounds 9, 108, and 125 except that Leu or Val rather than Ala is present in the first and last and/or the second and second-to-last positions of each compound, because such compounds are generically embraced by the WO Patent Application '948, because the substitution of leucine or valine for alanine is a conservative substitution of amino acids and a homologous substitution of amino acid sidechains which would not have been expected to materially affect the activity of the compounds, and because the resultant compounds have only the HIV protease inhibitory activity which would have been expected in view of the WO Patent Application '948 (see, e.g., page 31). The WO Patent Application '948's compounds have the same stereochemistry required by Applicants' claims, although the WO Patent Application '948 does not teach the compounds in stereochemically pure form. It would have been obvious to one of ordinary skill in the art at the

time Applicants' invention was made to form the stereochemically pure compounds of the WO Patent Application '948 as discussed above because it is desirable in the pharmaceutical arts to produce optically pure forms in order to avoid unwanted side effects from the other stereochemical forms and in order to increase the specific activity of the desired stereochemical forms, and because it is prima facie obvious to purify a known product. See MPEP 2144.04(VII).

12. Claim 23 is rejected under 35 U.S.C. 102(b) as being anticipated by the Huff article. The Huff article teaches compound 23 (see page 2313, Table V), which has the same structure and stereochemistry as the compound of instant claim 23.

13. Claim 3 is rejected under 35 U.S.C. 103(a) as being obvious over the Slee et al article. The Slee et al article teaches compound 8 (see page 11870, Figure 9), which has the same structure and stereochemistry as the compound of instant claim 3 in which R_1 is carbobenzyloxy and R_2 is -H(t-Butyl). The Slee et al article does not teach the compound in stereochemically pure form. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the stereochemically pure compound of the Slee et al article because it is desirable in the pharmaceutical arts to produce optically pure forms in order to avoid unwanted side effects from the other stereochemical forms and in order to increase the specific activity of the desired stereochemical forms, and because it is prima facie obvious to purify a known product. See MPEP 2144.04(VII).

14. Applicant's arguments filed June 28, 2001 have been fully considered but they are not persuasive.

The rejection over the European Patent Application '145 is maintained. It is irrelevant as to whether or not the European Patent Application '145 teaches away from having any additional amino acids at its N-terminus because the rejected claim does not require the presence of any additional amino acids at the corresponding position of Applicants' claimed inhibitors. Note that in Applicants' claims, R_1 can be hydrogen, just as is taught at page 10, lines 1-19, of the reference. Applicants characterize the European Patent Application '145's inclusion of proline as incidental. However, all of a reference's disclosure, and not just the reference's preferred embodiments, constitutes prior art which may be considered and applied against Applicants' claims. See MPEP 2123. In any event, the examiner does not agree with Applicants' characterization of the reference's disclosure of proline as "incidental". There are only five possibilities for X in the general formula at page 3, lines 25-32, of the reference, and with such a limited number of possibilities, the disclosure of X as possibly representing a methylene group is not "incidental". The disclosure of X as possibly representing a methylene group shows that the inventors of the European Patent Application '145 specifically desired to include peptides comprising proline residues. Note also that even with the choice of X as methylene in the European Patent Application '145, the resulting peptides still comprise an unnatural amino acid at their N-terminus. This unnatural amino acid, in combination with the C-terminal amidation taught at page 10, lines 1-19, of the reference would still result in a peptide which is resistant to digestive enzymes. The examiner's rejection is fully consistent with the disclosure of the European Patent Application '145.

Claim 3 remains rejected over Handa et al (although the citation in the rejection to Example 15 of Handa et al has been omitted because this example does not teach a prolinamide compound). Example 85 of Handa et al has the same stereochemistry required by Applicants' claim. Further, Handa et al suggest forming optically pure compounds, and the case law establishes the prima facie obviousness of purifying a known compound. Applicants have not probatively demonstrated that any unexpected properties arise from forming the stereochemically pure compound. Handa et al, in particular at column 5, lines 14-16, suggest that valine and cysteine are functional equivalents in the context of Handa et al's compounds.

Claim 1 remains rejected in view of the Tam et al article's compound 3. Note that claim 1 has not been amended to exclude the possibility that R_1 is carbobenzyloxy. With respect to the proviso inserted into claim 1, compound 3 of the Tam et al article comprises a substituent corresponding to Applicants' R_2 which is $-CH_2$-Phenyl and a substituent corresponding to Applicants' R_3 and R_4 which is a single combined oxygen forming a carbonyl group.

Claim 1 remains rejected over the WO Patent Application '100. Note that compound 17-R avoids the proviso clause inserted into claim 1 because in this compound, it is R_4, not R_2 or R_3, which is hydroxyl.

The rejection over the WO Patent Application '948 has been modified to address more of the claims, and to address the new limitation requiring stereochemically pure protease inhibitors. Applicants have not probatively demonstrated that any unexpected properties arise from forming the stereochemically pure compounds. Again, the reference itself suggests the substitutions at

various positions in the compounds which are pointed out in the rejection. All of the resulting compounds fall within the generic formula of the WO Patent Application '948 and would have been expected to share the retroviral protease inhibitory activity possessed by the class of compounds disclosed by the reference.

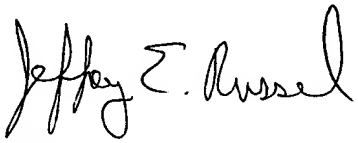
Jadhav et al is not applied against amended claims 10 and 11 because Jadhav et al do not specify the stereochemistry of their compounds 91 or 93, and therefore do not suggest the production of a stereochemically pure compound having the stereochemistry specified in Applicants' claims.

15. The references crossed off of the Information Disclosure Statement filed January 26, 2001 are duplicate citations.

16. Claims 6-9 and 19-22 are allowed. Claims 11 and 16-18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Christopher Low can be reached at (703) 308-2923. The fax number for Art Unit 1653 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 305-7401 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1653

JRussel

October 11, 2001